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(54) PHENYLEPHRINE-CONTAINING LIQUID FORMULATIONS

PHENYLEPHRIN ENTHALTENDE FLÜSSIGE FORMULIERUNGEN

FORMULATIONS LIQUIDES CONTENANT DE PHENYLÉPHRINE

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Description

FIELD OF THE INVENTION

[0001] An aqueous, oral liquid pharmaceutical composition comprising phenylephrine is provided. The composition is particularly well suited for the relief of cold, cough, flu, fever, headache, pain, body ache, migraine and allergy symptoms in pediatric patients.

BACKGROUND OF THE INVENTION

[0002] Orally administered pharmaceutical compositions are provided to patients in many dosage forms, including solid forms such as capsules, caplets or tablets and liquid forms such as solutions and suspensions. For many patients including young children, older persons and incapacitated persons, a liquid dose form is preferable because of the ease with which it may be swallowed.

[0003] Many liquid cough and cold compositions contain large amounts of sorbitol and other sugars, typically included to improve palatability. For example, U.S. Patent 5,730,997 discloses a composition containing about 20% to about 45% by weight sorbitol and about 10% to about 15% by weight hydrogenated maltose syrup. Such compositions are purported to improve palatability but high levels of sorbitol and maltose may contribute to the degradation of active ingredients such as phenylephrine, for example.

[0004] Accordingly, it would be desirable to have a palatable, liquid dosage form comprising phenylephrine with reduced propensity for degradation of all the available phenylephrine.

SUMMARY OF THE INVENTION

[0005] The pharmaceutical described herein is an aqueous oral pharmaceutical composition comprising phenylephrine, according to claim 1.

[0006] The composition may further comprise one or more second active agents selected from analgesics, decongestants, expectorants, anti-tussives, antipyretics, anti-inflammatory agents, cough suppressants and antihistamines.

[0007] The composition may be a solution. Suspension embodiments may further comprise viscosity modifying agents.

DETAILED DESCRIPTION OF THE INVENTION

[0008] The invention provides an oral, aqueous-based, liquid pharmaceutical composition comprising the pharmaceutical active phenylephrine. according to claim 1. The composition is palatable and has improved phenylephrine stability. The composition comprises phenylephrine, an artificial sweetener, up to about 45% w/v glycerin and up to about 10% w/v sorbitol. The glycerin to sorbitol ratio is about 2:1 to about 10:1. The inventors believe, without wishing to be bound to the theory, that the glycerin to sorbitol ratio is beneficial to both maintaining desirable organoleptic properties and reducing the opportunity for phenylephrine degradation. The composition of the invention may be a solution.

[0009] Preferably the phenylephrine is in a salt form. Suitable salt forms include, but are not limited to, phenylephrine hydrochloride (HCl), hydrobromide (HBr), bitartrate and tannate salts. Phenylephrine may be used in an amount of about 0.001% w/v to about 10% w/v. Preferably, phenylephrine is used in an amount of about 0.005% w/v to about 2.5%w/v. Herein % w/v means a percentage determined by the following formula:

$$\text{w/v \%} = \frac{\text{Weight of component (in grams)}}{\text{Volume of composition (in milliliters)}} \times 100 \quad (1)$$

Accordingly, for example, 1% w/v% phenylephrine means 1 gram of phenylephrine in 100 ml of the oral liquid composition.

[0010] An artificial sweetener is provided to improve palatability. An artificial sweetener is preferred for use as a sweetener to the use of conventional sugar sweeteners as the inventors believe, without wishing to be held to the theory, that conventional sugars may contribute to the degradation of phenylephrine in aqueous based compositions. Suitable artificial sweeteners, include but are not limited to sucralose, saccharine salts, cyclamates, acesulfame K, dipeptide based sweeteners, aspartame and mixtures thereof. Sucralose, which is a high intensity sweetener, is particularly well suited for use in the composition. Sucralose may be used in an amount of about 0.01% w/v to about 0.4% w/v, for example. The appropriate amount of artificial sweetener depends on properties and sweetness intensity of the artificial sweetener and target organoleptic properties of the composition. One skilled in the art is familiar with the characteristics of sweeteners and methods for determining amount of sweetener to be used.

[0011] Glycerin and sorbitol are used in the composition. In contrast to many conventional commercial cold products,

the composition contains more glycerin than sorbitol. The inventors believe, without wishing to be bound to the theory, that reduced amounts of sorbitol facilitate stability of the phenylephrine and that the glycerol to sorbitol ratio is important in achieving a stable, palatable composition. The composition may contain up to 45% w/v glycerin and up to about 10% w/v sorbitol. More preferably the composition may contain about 18% to about 30% w/v glycerin and about 3% to about 10% w/v sorbitol. Herein the amounts of sorbitol and glycerin are the amounts of standard commercial preparations of sorbitol and glycerin. Commercial sorbitol (as obtained from SPI Polyols, 321 Cherry Lane New Castle, Delaware 19720, or Roquette Frères 62080 Lestrew, France, for example) is an aqueous based composition which is 70% sorbitol. Commercial glycerin (as obtained from Dow Chemical Co., 2030 Dow Center, Midland, MI 48674, or Lyondell, 1221 McKinney St., Houston, TX 77253, for example) is 96% glycerin. One skilled in the art is familiar with these commercial preparations and methods of adjusting amounts should a different glycerin or sorbitol preparation be used.

[0012] The composition may contain one or more additional pharmaceutical actives (also referred to as "active(s)", "active agent(s)", "therapeutic agent(s)", "drug(s)"). Herein reference to "first pharmaceutical active" means phenylephrine and reference to "second pharmaceutical active" means any active other than phenylephrine. Further, the term second pharmaceutical active may refer to a single species of active or a plurality of species of actives other than phenylephrine (e.g., the total number of actives in the compositions may be greater than 2.) For embodiments of the composition which are solutions, any additional active should be water soluble. A water-soluble pharmaceutical active means a pharmaceutical active indicated to be soluble in water by the Merck Index. Additional actives in suspension embodiments may be water soluble, slightly soluble in water, or insoluble in an aqueous medium. It should be noted that second pharmaceutical actives are discussed herein in the context of compositions comprising phenylephrine, but aqueous based compositions having the sorbitol and glycerin ratios discussed herein may be likewise suitable for compositions comprising one or more of the second active agents in the absence of phenylephrine.

[0013] Suitable additional or second active agents include analgesics, decongestants, expectorants, anti-tussives, antipyretics, anti-inflammatory agents, cough suppressants and antihistamines.

[0014] Antihistamines useful in the practice of the present invention (along with their preferred salt form) include, but are not limited to, chlorpheniramine (maleate), brompheniramine (maleate); dexchlorpheniramine (maleate), dexbrompheniramine (maleate), triprolidine (HCl), diphenhydramine (HCl, citrate), doxylamine (succinate), triprolenamine (HCl), cyproheptadine (HCl), chlorcyclizine (HCl), bromodiphenhydramine (HCl), phenindamine (tartrate), pyrillamine (maleate, tannate), azatadine (maleate); acrivastine, astemizole, azelastine, cetirizine, ebastine, fexofenadine, ketotifen, carbinoxamine (maleate), desloratadine, loratadine, pheniramine maleate, thonzylamine (HCl), mizolastine and terfenadine.

[0015] Antitussives useful in the practice of the present invention (along with their preferred salt form) include, but are not limited to, chlorpheniramine, caramiphen (edylate), dextromethorphan (HBr), diphenhydramine (citrate, HCl, codeine (phosphate, sulfate) and hydrocodone.

[0016] Decongestants useful in the practice of the invention (along with their preferred salt form) include, but are not limited to, pseudoephedrine (HCl, sulfate), Ephedrine (HCl, Sulfate), phenylephrine (bitartrate, tannate, HBr, HCl), and phenylpropanolamine (HCl).

[0017] Expectorants which may be used in the practice of the invention (along with their preferred salt form) include but are not limited to terpin hydrate, guaifenesin (glycerol, guaiacolate), potassium (iodide, citrate) and potassium guaicolosulfonate.

[0018] Non-steroidal anti-inflammatory drugs (NSAIDS) which may be used in the practice of the invention include, but are not limited to, propionic acid derivatives such as ibuprofen, naproxen, ketoprofen, flurbiprofen, fenoprofen, suprofen, fluprofen and fenbufen; acetic acid derivatives such as tolmetin sodium, zomepirac, sulindac, and indomethacin; fenamic acid derivatives such as mefenamic acid and meclofenamate sodium; biphenyl carboxylic acid derivatives such as diflunisal and flufenisal and oxicams such as piroxicam, sudoxicam and isoxicam.

[0019] Cox 2 inhibitors which may be used in the practice of the invention include, but are not limited to, Celecoxib, Rofecoxib and Valdecoxib.

[0020] Analgesics which may be used in the practice of the invention include but are not limited to aspirin, acetaminophen, phenacetin and salicylate salts.

[0021] Examples of substantially insoluble pharmaceutical actives that may be suspended in the suspending system of suspension embodiments include, but are not limited to, nabumetone, glimepiride, diclofenac, piroxicam and meloxicam.

[0022] Of the pharmaceutically active compounds described above which may be included in addition to phenylephrine in the composition, those which are particularly preferred are set forth below along with preferred ranges for their inclusion into the claimed pharmaceutical composition.

[0023] Chlorpheniramine may be used in the pharmaceutical composition in amounts between about 0.01 w/v and about 0.05 w/v. Preferably chlorpheniramine, when used in the pharmaceutical composition, is present in the amount of about 0.01 w/v to 0.03 w/v.

[0024] Brompheniramine maleate may be used in the pharmaceutical composition, preferably in the amount of about 0.01 w/v to about 0.03w/v.

[0025] Dextromethorphan HBr may be used in the pharmaceutical composition, preferably in the amount of about 0.05 w/v to about 0.250 w/v.

[0026] Guaifenesin may be used in the composition in amounts of about 0.4 % w/v to about 6 % w/v and preferably in amounts of about 2 % w/v to about 4 % w/v.

[0027] Acetaminophen may be used in the composition in amounts of about 0.2 % w/v to about 10 % w/v and preferably in amounts of about 0.5 % w/v to about 3.2 % w/v.

[0028] Chlophendianol may be used in the composition in amounts of about 0.1 % w/v to about 1 % w/v and preferably in amounts of about 0.25 % w/v to about 0.5 % w/v.

[0029] Diphenhydramine may be used in the composition in amounts of about 0.2 % w/v to about 2 % w/v and preferably in amounts of about 0.5 % w/v to about 1 % w/v.

[0030] Brompheniramine may be used in the composition in amounts of about 0.016 % w/v to about 0.16% w/v and preferably in amounts of about 0.02% w/v to about 0.08 % w/v.

[0031] Loratadine may be used in the composition in amounts of about 0.02 % w/v to about 0.4 % w/v and preferably in amounts of about 0.1 % w/v to about 0.2 % w/v.

[0032] Aspirin may be used in the composition in amounts of about 0.8 % w/v to about 13 % w/v and preferably in amounts of about 3.2 % w/v to about 7.2 % w/v.

[0033] Doxylamine may be used in the composition in amounts of about 0.1 % w/v to about 1% w/v and preferably in amounts about 0.25 % w/v to about 0.5 % w/v.

[0034] Amounts of pharmaceutically active compounds incorporated are conventional dosages known to those skilled in the art. Further, for pharmaceutical compositions intended for use in the United States, amounts of pharmaceutical actives are preferably in compliance with applicable FDA regulations regarding dosage of such compounds.

[0035] The pharmaceutically active compounds are preferably of N.F. (National Formulary) or U.S.P. (United States Pharmacopeia) grade.

[0036] Excipients known by those skilled in the art may be useful in the practice of the present invention. Such excipients may include, but are not limited to, humectants such as propylene glycol, defoaming agents, buffers, electrolytes, preservatives such as sodium benzoate and disodium edetate, antioxidants, taste masking agents and various flavoring and coloring agents, for example.

[0037] Examples of suitable flavoring agents include, but are not limited to, natural and artificial flavors such as mints (i.e., peppermint, etc.), menthol, chocolate, artificial chocolate, bubblegum, both artificial and natural fruit flavors (i.e., cherry, grape, orange, strawberry, etc.) and combinations of two or more thereof. It is preferable to avoid flavoring agents which have aldehyde functional groups (e.g. use non-aldehyde containing flavorants is preferred). Flavoring agents are generally provided as a minor component of the composition in amounts effective to provide palatable flavor to the compositions. Typically, flavoring agents are present in amounts in the range of about 0 grams to about 5 grams per 100 ml of the composition.

[0038] Preservatives useful in the present invention include but are not limited to sodium benzoate, sorbates, such as potassium sorbate, salts of edetate (also known as salts of ethylenediaminetetraacetic acid or EDTA, such as disodium edetate), benzaldionium chloride and parabens (such as methyl, ethyl, propyl, and butyl p-hydroxybenzoic acid esters). Preservatives listed above are exemplary, but each preservative must be evaluated on an experimental basis, in each formulation to assure compatibility and efficacy of the preservative. Methods for evaluating the efficacy of preservatives in pharmaceutical formulations are known to those skilled in the art. Sodium benzoate and disodium edetate are the presently preferred preservative ingredients.

[0039] Preservatives are generally present in amounts of up to one gram per 100 ml of the pharmaceutical composition. Preferably the preservatives are present in amounts in the range of from about 0.01 w/v to about 0.4 w/v of the composition. Typically, the preservative sodium benzoate would be present in the range of about 0.1 w/v to about 0.2 w/v of the composition, for example. Sodium benzoate was used in a concentration of about 0.1 w/v in an exemplary embodiment of the composition.

[0040] Propylgallate is exemplary of an antioxidant that is suitable for use in the composition.

[0041] Sodium citrate is exemplary of a buffering agent which may be used in the composition. It is preferable to buffer the composition to maintain the pH less than about 5.4. More preferably the pH may be maintained in the range of about pH 2 to about pH 4.5.

[0042] Coloring agents may also be incorporated in the pharmaceutical composition to provide an appealing color to the composition. The coloring agents should be selected to avoid chemical incompatibilities with other ingredients in the composition. Suitable coloring agents are well known to those skilled in the art.

[0043] In some embodiments, particularly suspension embodiments, a surface-modifying agent, such as a surfactant, may be used in the pharmaceutical composition to modify the surface of the suspended components. Such surface modification is believed to facilitate diminished irreversible aggregation of the suspended particles. The surfactant may be an ionic or non-ionic surfactant or mixtures thereof. Exemplary surfactants include but are not limited to polysorbates (tweens), Spans™, togats, lecithin, polyoxyethylene-polyoxypropylene block copolymers and medium chain mono/di-

glycerides.

[0044] Typically, suspension embodiments will further comprise a viscosity modifying agents. Suitable viscosity modifying agents include but are not limited to chitosan, xanthan, hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), hydroxyethylcellulose (HEC), galactomannans such as guar, konjac, locust bean gum and mamman, for example, microcrystalline cellulose and combinations thereof.

[0045] Xanthan gums suitable for use in the present invention are high molecular weight polysaccharides such as the xanthan gum produced by *Xanthomonas campestris*, for example. Xanthan gum is an article of commerce and is available, for example, from manufacturers such as: Rhodia, Inc. under the brand name Rhodigel™ and from Kelco™, a division of Merck. Rhodigel™ 80 Pharm Grade is exemplary of one specific commercial product suitable for use in the practice of the invention.

[0046] Microcrystalline cellulose is commercially available from suppliers such as FMC (1735 Market Street, Philadelphia, PA 19103) under the tradename Avicel™

[0047] The amount of viscosity modifier used depends on the desired "thickness" of the composition and the type viscosity modifier used. Combinations of viscosity modifiers may be employed. For example, in an exemplary embodiment with a viscosity of about 1500 to about 4500 cps, up to about 1.0 w/v xanthan gum may be used with up to about 3.0 w/v microcrystalline cellulose may be as a viscosity modifier.

[0048] It is preferable to avoid viscosity modifiers with a significant presence of negatively charged moieties or moieties with propensity to ionize to a negative charge if the structure of the modifier is such that the negatively charged moiety is readily available for reaction.

[0049] Suspensions are useful for preparing compositions comprising actives that are substantially insoluble in water. In suspension embodiments the phenylephrine is dissolved in the aqueous medium. The composition may contain one or more second active agents dissolved in the aqueous medium and/or one or more substantially water insoluble second active agents may be suspended in the composition. For the suspension embodiments, it is preferable that both the suspended substantially insoluble active ingredients and any soluble active ingredients dissolved in the aqueous medium, are distributed to form a substantially homogeneous distribution of active ingredients in the pharmaceutical composition.

[0050] Exemplary pharmaceutical actives that are substantially insoluble in the aqueous composition and would be expected to form suspension include but are not limited to Ibuprofen, Ketoprofen, Naproxen, Celecoxib, Rofecoxib, Valdecoxib, Nabumetone, Glimepiride, Diclofenac, Piroxicam and Meloxicam. For pharmaceutical actives not specified on this list a pharmaceutical active substantially insoluble in the aqueous composition means a pharmaceutical active designated as relatively insoluble or insoluble in water by the Merck Index.

[0051] Typically, the composition is provided to a patient in need of treatment in a dosage unit of 5 ml although other dosage units may be likewise suitable. The dosage unit may be provided as a single dosage unit or multiples thereof, based on age, weight and other health parameters determined by a physician to be relevant.

EXAMPLE 1

[0052] An exemplary composition comprising the single first pharmaceutical active phenylephrine is provided in Table 1. This composition is representative and one of many composition that are within the scope of the invention. The exemplary embodiment is provided for illustrative purposes.

Table 1

Ingredient	Amount (grams/100ml x 100)
Phenylephrine HCl	0.05% w/v
Glycerin (96% USP)	25% w/v
Sorbitol (70% Solution USP)	10% w/v
Citric Acid	0.75 % w/v
Micronized Sucralose Powder (NF)	0.2% w/v
menthol	0.02% w/v
propylene glycol	1.3% w/v
colorant	0.01% w/v
sodium citrate	0.15% w/v

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(continued)

Ingredient	Amount (grams/100ml x 100)
sodium benzoate	0.1% w/v
purified H ₂ O USP	sufficient quantity to make final volume

[0053] The composition of Table 1 may be prepared by simple mixing. The ingredients are mixed in a vessel equipped with a mechanical stirrer (e.g., a lightnin mixer), the vessel is calibrated and marked to designate the final volume. An aliquot of water substantially less than the target final volume is placed in the vessel and the other ingredient are added sequentially with mixing. Colorants are premixed with a small amount of water prior to addition to the main. Likewise, menthol and propylene glycol, are premixed before addition to the main vessel. After all other ingredients have been added and mixed sufficiently to dissolve, water is added to bring the total volume of the composition to the predetermined final volume and mixing was continued for approximately 10 minutes.

EXAMPLE 2

[0054] An exemplary composition comprising phenylephrine and a second active Brompheniramine maleate is provided in Table 2. This composition is representative and one of the many compositions that are within the scope of the invention. The exemplary embodiment is provided for illustrative purposes.

Table 2

Ingredient	Amount (grams/100ml x 100)
Phenylephrine HCl	0.05% w/v
Brompheniramine Maleate	0.02% w/v
Glycerin (96% USP)	25% w/v
Sorbitol (70% Solution USP)	10% w/v
Citric Acid	0.75 % w/v
Micronized Sucralose	0.2% w/v
Artificial Fruit Flavor	0.2% w/v
Colorant	< 0.1% w/v
Sodium Citrate	0.10% w/v
Sodium Benzoate	0.1% w/v
Purified H ₂ O	Sufficient quantity to make final volume

[0055] The composition of Table 2 may be prepared using the manner of preparation described in Example 1.

EXAMPLE 3

[0056] Stability data for compositions comprising phenylephrine are provided in Tables 3 and 4. Compositions comprising 0.05% w/v of phenylephrine in an aqueous based composition using the conventional commercial proportions of 25% w/v to 40% w/v sorbitol and the composition of one embodiment of the invention comprising 0.05% w/v phenylephrine in an aqueous based composition using the proportion of 25% glycerin to 10% sorbitol were prepared and subjected to stability testing. The compositions were alike in all other respects except the glycerin to sorbitol ratio.

[0057] Table 3 shows the results of stability testing over one month at conditions of 60°C and 60% relative humidity (herein "60/60"). Table 4 shows the results of stability testing over six months at conditions of 40°C and 75% relative humidity (herein "40/75"). For both Table 3 and 4, stability was assessed as the amount of phenylephrine degradants present as compared to amount of phenylephrine at the indicated time point. At the indicated time points, samples of the composition were analyzed by HPLC (high pressure liquid chromatography) and the total peak area attributed to

phenylephrine degradants was compared to the peak area of Phenylephrine. Accordingly, the percentages reported in Tables 3 and 5 are percentages based on the total peak area of all phenylephrine degradants to the peak area of phenylephrine for the sample analyzed.

Table 3

Time (months)	Phenylephrine Degradants Gly:Sorb 25:48	Phenylephrine Degradants Gly:Sorb 25:10
0	0.07	0
0.25	0.26	0
0.5	0.72	0
1	1.37	.029

Table 4

Time (months)	Phenylephrine Degradants Gly:Sorb 25:48	Phenylephrine Degradants Gly:Sorb 25:10
0	0.07	0
1	0.08	0
2	0.16	0
3	0.12	0
6	0.4	0

[0058] As Table 3 shows under conditions of 60/60 no phenylephrine degradants were detected in the composition of the invention for the first three weeks of the study and only 0.29% phenylephrine degradants were detected at the end of the fourth week of the study. In contrast phenylephrine degradants were observed at every test point for the conventional composition with 1.37% phenylephrine degradants detected at the end of the fourth week of the study.

[0059] As Table 4 shows, under conditions of 40/75, no phenylephrine degradants were observed over the six-month course of the study for the composition of the invention. In contrast phenylephrine degradants were observed at every test point for the conventional composition with 0.4% phenylephrine degradants at the end of the sixth month of the study.

Claims

1. An aqueous oral pharmaceutical composition which is a solution comprising:

- a). phenylephrine;
- b). artificial sweetener;
- c). up to 45% w/v glycerin; and
- d). up to 10% w/v sorbitol wherein the glycerin to sorbitol ratio is from about 2:1 to about 10:1.

2. The composition of claim 1, wherein the glycerin to sorbitol ratio is from 2:1 to 5:1.

3. The composition of claim 1 or claim 2, wherein the artificial sweetener is selected from the group consisting of sucralose, saccharine salts, cyclamates, acesulfame K, dipeptide based sweeteners, aspartame and mixtures thereof.

4. The composition of claim 3, where in the artificial sweetener comprises sucralose.

5. The composition of any one of claims 1 to 4, further comprising a flavor system.

6. The composition of claim 5, wherein the flavor system includes non-aldehyde flavorants.

7. The composition of any one of claims 1 to 6, further comprising at least one second active agent selected from the group consisting of analgesics, decongestants, expectorants, anti-tussives, antipyretics, anti-inflammatory agents, cough suppressants and antihistamines.

8. The composition of claim 7, wherein the second active agent is selected from the group consisting of non-steroidal anti-inflammatory drugs (NSAIDS), propionic acid derivatives, flurbiprofen, fenoprofen, suprofen, fluprofen, fenbufen; acetic acid derivatives, tolmetin sodium, zomepirac, sulindac, indomethacin, fenamic acid derivatives, mefenamic acid, meclofenamate sodium, biphenyl carboxylic acid derivatives, diflunisal, flufenisal, oxicams, sudoxicam, isoxicam, chlorpheniramine, brompheniramine; dexchlorpheniramine, dexbrompheniramine, triprolidine, chlorcyclizine, diphenhydramine, doxylamine, triprolenamine, cyproheptadine, bromodiphenhydramine, phenindamine, pyrilamine, azatadine, acrivastine, astemizole, azelastine, cetirizine, ebastine, fexofenadine, ketotifen, carbinoxamine, desloratadine, loratadine, pheniramine, thonzylamine, mizolastine, terfenadine, chlorpheniramine, carbamiphen, dextromethorphan, diphenhydramine, codeine, hydrocodone, pseudoephedrine, ephedrine, phenylpropenolamine, terpin hydrate, guaifenesin, potassium, potassium guaicol sulfonate, aspirin, acetaminophen, phenacetin, salicylate salts and combination thereof.

9. The composition of claim 7, wherein the at least one second active agent is selected from the group consisting of chlorpheniramine, dextromethorphan, guaifenesin, acetaminophen, chlorpheniramine, diphenhydramine, brompheniramine, loratadine, aspirin and doxylamine succinate.

10. The composition of any one of claims 1 to 9, further comprising a buffering agent.

11. The composition of claim 10, wherein the buffering agent maintains a pH below 5.4 in the composition.

12. The composition of claim 10, wherein the buffering agent maintains a pH from 2 to 4.5 in the composition.

13. The composition of any one of claims 1 to 12, further comprising a preservative.

14. The composition of claim 13, wherein the preservative is selected from the group consisting of sodium benzoate, sorbates, parabens, EDTA and combinations thereof.

15. The composition of any one of claims 1 to 14, further comprising an antioxidant.

16. The composition of claim 15, wherein the antioxidant is propyl gallate.

17. An aqueous pharmaceutical solution according to claim 1 comprising:

- a). phenylephrine;
- b). artificial sweetener;
- c). 18% to 30% w/v glycerin; and
- d). 3% to 10% w/v sorbitol, wherein the glycerin to sorbitol ratio is from about 2:1 to about 10:1.

18. The solution of claim 17, wherein the glycerin to sorbitol ratio is from 2:1 to 5:1.

19. The solution of claim 17 or claim 18, wherein the artificial sweetener is selected from the group consisting of sucralose, saccharine salts, cyclamates, acesulfame K, dipeptide based sweeteners, aspartame and mixtures thereof.

20. The solution of claim 19, wherein the artificial sweetener comprises sucralose.

21. The solution of any one of claims 17 to 20, further comprising an effective amount of at least one second active agent selected from the group consisting of analgesics, decongestants, expectorants, anti-tussives, antipyretics, anti-inflammatory agents, cough suppressants and antihistamines.

22. The solution of claim 21, wherein the second active agent is selected from the group consisting of non-steroidal anti-inflammatory drugs (NSAIDS), propionic acid derivatives, flurbiprofen, fenoprofen, suprofen, fluprofen, fenbufen; acetic acid derivatives, tolmetin sodium, zomepirac, sulindac, indomethacin, fenamic acid derivatives, mefenamic acid, meclofenamate sodium, biphenyl carboxylic acid derivatives, diflunisal, flufenisal, oxicams, sudoxicam, isoxicam, chlorpheniramine, brompheniramine; dexchlorpheniramine, dexbrompheniramine, triprolidine, chlorcyclizine,

diphenhydramine, doxylamine, tripelenamine, cyproheptatine, bromodiphenhydramine, phenindamine, pyrillamine, azatadine, acrivastine, astemizole, azelastine, cetirizine, ebastine, fexofenadine, ketotifen, carbinoxamine, desloratadine, loratadine, pheniramine, thonzylamine, mizolastine, terfenadine, chlophendianol, caramiphen, dextromethorphan, diphenhydramine, codeine, hydrocodone, pseudoephedrine, ephedrine, phenylpropenolamine, terpin hydrate, guaifenesin, potassium, potassium guaicol sulfonate, aspirin, acetaminophen, phenacetin, salicylate salts and combination thereof.

23. The solution of claim 22, wherein the at least one second active agent is selected from the group consisting of chlorpheniramine, dextromethorphan, guaifenesin, acetaminophen, chlophendianol, diphenhydramine, brompheniramine, loratadine, aspirin and doxylamine succinate.

24. The solution of any one of claims 17 to 23, further comprising up to 1.25% w/v citric acid.

25. The solution of any one of claims 17 to 24, further comprising up to 0.2% w/v propyl gallate.

Patentansprüche

1. Wässrige orale pharmazeutische Zusammensetzung, welche eine Lösung ist, die umfasst:

- a). Phenylephrin;
- b). künstliches Süßungsmittel;
- c). bis zu 45% G/V Glycerin; und
- d). bis zu 10% G/V Sorbit, wobei das Glycerin-zu-Sorbit-Verhältnis von etwa 2:1 bis etwa 10:1 reicht.

2. Zusammensetzung gemäß Anspruch 1, wobei das Glycerin-zu-Sorbit-Verhältnis von 2:1 bis 5:1 reicht.

3. Zusammensetzung gemäß Anspruch 1 oder Anspruch 2, wobei das künstliche Süßungsmittel ausgewählt ist aus der Gruppe, bestehend aus Sucralose, Saccharinsalzen, Cyclamaten, Acesulfam K, Dipeptid-basierenden Süßungsmitteln, Aspartam und Mischungen davon.

4. Zusammensetzung gemäß Anspruch 3, wobei das künstliche Süßungsmittel Sucralose umfasst.

5. Zusammensetzung gemäß einem der Ansprüche 1 bis 4, die weiterhin ein Aromasystem umfasst.

6. Zusammensetzung gemäß Anspruch 5, wobei das Aromasystem nicht-Aldehyd-Aromastoffe umfasst.

7. Zusammensetzung gemäß einem der Ansprüche 1 bis 6, die weiterhin wenigstens ein zweites aktives Mittel, ausgewählt aus der Gruppe, bestehend aus Analgetika, Dekongestionsmitteln, Expektorantien, Antitussiva, Antipyretika, entzündungshemmenden Mitteln, Hustenstillern und Antihistaminen, umfasst.

8. Zusammensetzung gemäß Anspruch 7, wobei das zweite aktive Mittel ausgewählt ist aus der Gruppe, bestehend aus nicht-steroidalen Antirheumatika (NSAR), Propionsäurederivaten Flurbiprofen, Fenoprofen, Suprofen, Fluprofen, Fenbufen; Essigsäurederivaten, Tolmetin-Natrium, Zomepirac, Sulindac, Indomethacin, Fenaminsäurederivaten, Mefenaminsäure, Meclofenamat-Natrium, Biphenylcarbonsäurederivaten, Diflunisal, Flufenisal, Oxicamen, Sudoxicam, Isoxicam, Chlorpheniramin, Brompheniramin, Dexchlorpheniramin, Dexbrompheniramin, Triprolidin, Chlorcyclizin, Diphenhydramin, Doxylamin, Tripelenamin, Cyproheptatin, Bromdiphenhydramin, Phenindamin, Pyrillamin, Azatadin, Acrivastin, Astemizol, Azelastin, Cetirizin, Ebastin, Fexofenadin, Ketotifen, Carbinoxamin, Desloratadin, Loratadin, Pheniramin, Thonzylamin, Mizolastin, Terfenadin, Chlophendianol, Caramiphen, Dextromethorphan, Diphenhydramin, Codein, Hydrocodon, Pseudoephedrin, Ephedrin, Phenylpropenolamin, Terpinhydrat, Guaifenesin, Kalium, Kaliumguaiaicolsulfonat, Aspirin, Acetaminophen, Phenacetin, Salicylsalzen und Kombinationen davon.

9. Zusammensetzung gemäß Anspruch 7, wobei das wenigstens eine zweite aktive Mittel ausgewählt ist aus der Gruppe, bestehend aus Chlorpheniramin, Dextromethorphan, Guaifenesin, Acetaminophen, Chlophendianol, Diphenhydramin, Brompheniramin, Loratadin, Aspirin und Doxylaminsuccinat.

10. Zusammensetzung gemäß einem der Ansprüche 1 bis 9, die weiterhin ein Puffermittel umfasst.

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11. Zusammensetzung gemäß Anspruch 10, wobei das Puffermittel einen pH unterhalb von 5,4 in der Zusammensetzung aufrechterhält.
12. Zusammensetzung gemäß Anspruch 10, wobei das Puffermittel einen pH von 2 bis 4,5 in der Zusammensetzung aufrechterhält.
13. Zusammensetzung gemäß einem der Ansprüche 1 bis 12, die weiterhin ein Konservierungsmittel umfasst.
14. Zusammensetzung gemäß Anspruch 13, wobei das Konservierungsmittel ausgewählt ist aus der Gruppe, bestehend aus Natriumbenzoat, Sorbaten, Parabenen, EDTA und Kombinationen davon.
15. Zusammensetzung gemäß einem der Ansprüche 1 bis 14, die weiterhin ein Antioxidationsmittel umfasst.
16. Zusammensetzung gemäß Anspruch 15, wobei das Antioxidationsmittel Propylgallat ist.
17. Wässrige pharmazeutische Lösung gemäß Anspruch 1, die umfasst:
- a). Phenylephrin;
 - b). künstliches Süßungsmittel;
 - c). 18% bis 30% G/V Glycerin und
 - d). 3% bis 10% G/V Sorbit, wobei das Glycerin-zu-Sorbit-Verhältnis von etwa 2:1 bis etwa 10:1 reicht.
18. Lösung gemäß Anspruch 17, wobei das Glycerin-zu-Sorbit-Verhältnis von 2:1 bis 5:1 reicht.
19. Lösung gemäß Anspruch 17 oder Anspruch 18, wobei das künstliche Süßungsmittel ausgewählt ist aus der Gruppe, bestehend aus Sucralose, Saccharinsalzen, Cyclamaten, Acesulfam K, Dipeptid-basierenden Süßungsmitteln, Aspartam und Mischungen davon.
20. Lösung gemäß Anspruch 19, wobei das künstliche Süßungsmittel Sucralose umfasst.
21. Lösung gemäß einem der Ansprüche 17 bis 20, die weiterhin eine wirksame Menge wenigstens eines zweiten aktiven Mittels, ausgewählt aus der Gruppe, bestehend aus Analgetika, Dekongestionsmitteln, Expektorantien, Antitussiva, Antipyretika, entzündungshemmenden Mitteln, Hustenstillern und Antihistaminen, umfasst.
22. Lösung gemäß Anspruch 21, wobei das zweite aktive Mittel ausgewählt ist aus der Gruppe, bestehend aus nicht-steroidalen Antirheumatika (NSAR), Propionsäurederivaten-Flurbiprofen, Fenoprofen, Suprofen, Fluprofen, Fenbufen; Essigsäurederivaten, Tolmetin-Natrium, Zomepirac, Sulindac, Indomethacin, Fenaminsäurederivaten, Mefenaminsäure, Meclofenamat-Natrium, Biphenylcarbonsäurederivaten, Diflunisal, Flufenisal, Oxicamen, Sudoxicam, Isoxicam, Chlorpheniramin, Brompheniramin, Dexchlorpheniramin, Dexbrompheniramin, Triprolidin, Chlorcyclizin, Diphenhydramin, Doxylamin, Tripelenamin, Cyproheptatin, Bromdiphenhydramin, Phenindamin, Pyrilamin, Azatadin, Acrivastin, Astemizol, Azelastin, Cetirizin, Ebastin, Fexofenadin, Ketotifen, Carbinoxamin, Desloratadin, Loratadin, Pheniramin, Thonzylamin, Mizolastin, Terfenadin, Chlophendiol, Caramiphen, Dextromethorphan, Diphenhydramin, Codein, Hydrocodon, Pseudoephedrin, Ephedrin, Phenylpropanolamin, Terpinhydrat, Guaifenesin, Kalium, Kaliumguaiaacolsulfonat, Aspirin, Acetaminophen, Phenacetin, Salicylsalzen und Kombinationen davon.
23. Lösung gemäß Anspruch 22, wobei das wenigstens eine zweite aktive Mittel ausgewählt ist aus der Gruppe, bestehend aus Chlorpheniramin, Dextromethorphan, Guaifenesin, Acetaminophen, Chlophendiol, Diphenhydramin, Brompheniramin, Loratadin, Aspirin und Doxylaminsuccinat.
24. Lösung gemäß einem der Ansprüche 17 bis 23, die weiterhin bis zu 1,25% G/V Zitronensäure umfasst.
25. Lösung gemäß einem der Ansprüche 17 bis 24, die weiterhin bis zu 0,2% G/V Propylgallat umfasst.

Revendications

1. Composition pharmaceutique orale aqueuse qui est une solution comprenant :

- a). de la phényléphrine ;
- b). un édulcorant artificiel ;
- c). jusqu'à 45 % p/v de glycérine ; et
- d). jusqu'à 10 % p/v de sorbitol dans laquelle le rapport de la glycérine au sorbitol est d'environ 2:1 à environ 10:1.

2. Composition selon la revendication 1, dans laquelle le rapport de la glycérine au sorbitol est de 2:1 à 5:1.
3. Composition selon la revendication 1 ou la revendication 2, dans laquelle l'édulcorant artificiel est choisi dans le groupe constitué de sucralose, sels de saccharine, cyclamates, acésulfame K, édulcorants à base de dipeptides, aspartame et leurs mélanges.
4. Composition selon la revendication 3, dans laquelle l'édulcorant artificiel comprend du sucralose.
5. Composition selon l'une quelconque des revendications 1 à 4, comprenant en outre un système d'arôme.
6. Composition selon la revendication 5, dans laquelle le système d'arôme comprend des aromatisants non aldéhydiques.
7. Composition selon l'une quelconque des revendications 1 à 6, comprenant en outre au moins un second agent actif choisi dans le groupe constitué d'analgésiques, décongestionnants, expectorants, antitussifs, antipyrétiques, agents anti-inflammatoires, supprimeurs de la toux et antihistaminiques.
8. Composition selon la revendication 7, dans laquelle le second agent actif est choisi dans le groupe constitué de médicaments anti-inflammatoires non stéroïdiens (AINS), dérivés de l'acide propionique, flurbiprofène, fénoprofène, suprofène, fluprofène, fenbufène ; dérivés de l'acide acétique, tolmétine sodique, zomépirac, sulindac, indométacine, dérivés de l'acide fénamique, acide méfénamique, méclofénamate de sodium, dérivés d'acide biphenyl-carboxylique, diflunisal, flufénisal, oxicams, sudoxicam, isoxicam, chlorphéniramine, bromphéniramine ; dexchlorphéniramine, dexbromphéniramine, triprolidine, chlorcyclizine, diphenhydramine, doxylamine, tripelénamine, cyproheptadine, bromodiphenhydramine, phénindamine, pyrilamine, azatadine, acrivastine, astémizole, azélastine, cétirizine, ébastine, fexofénadine, kétotifène, carbinoxamine, desloratadine, loratadine, phéniramine, thonzylamine, mizolastine, terfénadine, chlorphédianol, caramiphène, dextrométhorphan, diphenhydramine, codéine, hydrocodone, pseudoéphédrine, éphédrine, phénylpropanolamine, hydrate de terpène, guaïfénésine, potassium, guaïacolsulfonate de potassium, aspirine, acétaminophène, phénacétine, sels salicylés et leurs combinaisons.
9. Composition selon la revendication 7, dans laquelle l'au moins un second agent actif est choisi dans le groupe constitué de chlorphéniramine, dextrométhorphan, guaïfénésine, acétaminophène, chlorphédianol, diphenhydramine, bromphéniramine, loratadine, aspirine et succinate de doxylamine.
10. Composition selon l'une quelconque des revendications 1 à 9, comprenant en outre un agent tampon.
11. Composition selon la revendication 10, dans laquelle l'agent tampon maintient un pH au-dessous de 5,4 dans la composition.
12. Composition selon la revendication 10, dans laquelle l'agent tampon maintient un pH de 2 à 4,5 dans la composition.
13. Composition selon l'une quelconque des revendications 1 à 12, comprenant en outre un conservateur.
14. Composition selon la revendication 13, dans laquelle le conservateur est choisi dans le groupe constitué de benzoate de sodium, sorbates, parabènes, EDTA et leurs combinaisons.
15. Composition selon l'une quelconque des revendications 1 à 14, comprenant en outre un antioxydant.
16. Composition selon la revendication 15, dans laquelle l'antioxydant est le gallate de propyle.
17. Solution pharmaceutique aqueuse selon la revendication 1 comprenant :
 - a). de la phényléphrine ;
 - b). un édulcorant artificiel ;

c). 18 à 30 % p/v de glycérine ; et

d). 3 à 10 % p/v de sorbitol, dans laquelle le rapport de la glycérine sur le sorbitol est d'environ 2:1 à environ 10:1.

18. Solution selon la revendication 17, dans laquelle le rapport de la glycérine au sorbitol est de 2:1 à 5:1.

19. Solution selon la revendication 17 ou la revendication 18, dans laquelle l'édulcorant artificiel est choisi dans le groupe constitué de sucralose, sels de saccharine, cyclamates, acésulfame K, édulcorants à base de dipeptides, aspartame et leurs mélanges.

20. Solution selon la revendication 19, dans laquelle l'édulcorant artificiel comprend du sucralose.

21. Solution selon l'une quelconque des revendications 17 à 20, comprenant en outre une quantité efficace d'au moins un second agent actif choisi dans le groupe constitué d'analgésiques, décongestionnants, expectorants, antitussifs, antipyrétiques, agents anti-inflammatoires, supprimeurs de la toux et antihistaminiques.

22. Solution selon la revendication 21, dans laquelle le second agent actif est choisi dans le groupe constitué de médicaments anti-inflammatoires non stéroïdiens (AINS), dérivés de l'acide propionique, flurbiprofène, fénopropène, suprofène, fluprofène, fenbufène ; dérivés de l'acide acétique, tolmétine sodique, zomépirac, sulindac, indométacine, dérivés de l'acide fénamique, acide méfénamique, méclofénamate de sodium, dérivés d'acide biphenyl-carboxylique, diflunisal, flufénisal, oxicams, sudoxicam, isoxicam, chlorphéniramine, bromphéniramine ; dexchlorphéniramine, dexbromphéniramine, triprolidine, chlorcyclizine, diphenhydramine, doxylamine, tripélénamine, cyproheptadine, bromodiphenhydramine, phénindamine, pyrilamine, azatadine, acrivastine, astémizole, azélastine, cétirizine, ébastine, fexofénadine, kétotifène, carbinoxamine, desloratadine, loratadine, phéniramine, thonzylamine, mizolastine, terfénadine, chlorphédianol, caramiphène, dextrométhorphan, diphenhydramine, codéine, hydrocodone, pseudoéphédrine, éphédrine, phénylpropanolamine, hydrate de terpine, guaïfénésine, potassium, guaïacolsulfonate de potassium, aspirine, acétaminophène, phénacétine, sels salicylés et leurs combinaisons.

23. Solution selon la revendication 22, dans laquelle l'au moins un second agent actif est choisi dans le groupe constitué de chlorphéniramine, dextrométhorphan, guaïfénésine, acétaminophène, chlorphédianol, diphenhydramine, bromphéniramine, loratadine, aspirine et succinate de doxylamine.

24. Solution selon l'une quelconque des revendications 17 à 23, comprenant en outre jusqu'à 1,25 % p/v d'acide citrique.

25. Solution selon l'une quelconque des revendications 17 à 24, comprenant en outre jusqu'à 0,2 % p/v de gallate de propyle.

REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

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